REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 3, 4, 8-11, 16 and 19 are in the case. The number of claims has been reduced, and the amendments effected (discussed below) do not introduce any new issues or new matter. Entry and favorable consideration of the claims as amended at this stage of prosecution are respectfully requested.

I. THE OBVIOUSNESS REJECTION

Claims 1, 3, 4, 6, 8-11, 16 and 19 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Friedlos et al., *J. Med. Chem.* 1997, 1270-1275 in view of Patani et al., *Chem. Rev.* 1996, 3147-3176. That rejection is respectfully traversed.

In response, and without conceding to any merit which might reside in this rejection, claims 1 and 6 have been canceled without prejudice. The obviousness rejection as it was applied to those claims has accordingly been rendered moot.

The remaining claims have been amended to cover compounds of formula IIIb as set forth in claim 4. Formula IIIb covers a subset of compounds of formula IIb, in which A and B are bromine and mesylate. Subject matter cancelled by the present amendment has been deleted without prejudice to pursuing that subject matter in a separate continuing application. For the reasons given below, it is believed that the invention as now claimed is clearly patentably distinguished over the art of record.

Referring to Friedlos, the Action expressly identifies compounds 12-16 of Friedlos as the closest compounds to those presently claimed. The presently claimed compounds are patentable over those compounds for the following reasons.

One of ordinary skill would not have been motivated to arrive at the presently claimed compounds based on compounds 12-16 of Friedlos. In particular, there is no disclosure or suggestion in Friedlos which would have led a chemist to modify the Friedlos compounds 12-16 in a way such that the claimed compounds would have been produced or suggested. In other words, there is nothing in Friedlos that would have "suggested making the specific molecular modifications necessary to achieve the claimed invention" (*In re* Deuel, 51 F. 3d 1552, 1558 (Fed. Cir. 1995)).

It is Applicants' position that the prior art in general and Friedlos in particular fails to provide any such suggestion to one of ordinary skill. A chemist would not have been motivated to modify compounds 12-16 in the manner required to obtain the bromomesylate compounds of formula IIIb as now claimed. The modification proposed would involve abandoning the symmetric structure in which both X and Y are the same to move to an asymmetric structure in which X and Y must be different. There is no suggestion in Friedlos to do that, and there would have been no motivation on the part of the skilled artisan to effect that modification. Indeed, such a structural modification is contrary to the entire disclosure of Friedlos in which it is only compounds in which X and Y are the **same** that are sufficiently potent. That potency is in complete contrast to the only example of a compound in Friedlos in which X and Y are different, compound 6. Compound 6 was expressly referenced as insufficiently potent to allow a full data set to be collected (see, page 1272). This lack of potency of the only compound described in Friedlos having different values for X and Y provides no motivation to even explore such asymmetric compounds further, much less with any expectation of viable activity. The data provided for compound 6 in fact leads **away** from the invention now claimed.

Absent any such motivation, no *prima facie* case of obviousness is generated in this case.

The lack of potency of compound 6 and its implications were discussed in the previous response in this case. The Examiner has responded by arguing that this lack of potency is due to the values for X and Y in compound 6 (chlorine and mesylate), which the Examiner refers to as the least potent substituents for this system. The Examiner also asserts that replacing the weaker chlorine with bromine or iodine would lead to a more potent drug. This position is respectfully traversed for the following reasons.

First, the Examiner is now referring to a modification to compound 6, whereas he has expressed his view that compounds 12-16 are the closest prior art. It is the motivation to make modifications to the closest compounds of the prior art which is most relevant here, as even replacement of a chlorine by a bromine or iodine in compound 6 would not result in or suggest a compound of formula IIIb as now claimed. Thus, replacement of a chlorine with an iodine would not lead to a bromomesylate mustard as now claimed. Further, even the replacement of a chlorine with a bromine would not be enough - formula IIIb requires X and Y to be *meta* to each other, whereas the corresponding groups for compound 6 are *para* to each other. To move from compound 6 to a compound of formula IIIb would therefore require two structural modifications rather than one, neither of which are suggested by the Friedlos.

It is further noted that replacement of a chlorine with a bromine or iodine in either compound 12 or compound 15 would not yield a bromomesylate compound of formula IIIb now claimed. It would only be the replacement of a bromine by a mesylate in

compound 13 which would achieve that. However, with regard to the possible replacement of a bromine with a mesylate to move from compound 13 to a bromomesylate compound of the present invention, it is clear that there would have been no motivation for one of ordinary skill, based on Friedlos, to replace a bromine with a mesylate or to substitute a mesylate for any other substituent. Indeed, based on Friedlos, mesylate would be the last substituent to be selected in an attempt to produce a more active compound. None of the compounds described by Friedlos which have mesylate as a value for X or Y are reported as sufficiently potent, whether symmetric or asymmetric in structure. In fact, when the data for compound 4 (in which X and Y are chlorine) is compared to the data for compound 6 (in which one chlorine is replaced by mesylate) and to that for compound 7 (in which both chlorines are replaced by mesylate), the substitutions lead to compounds with poorer activity (see Table 1). In combination, this suggests an "anything but mesylate" approach to modification in order to obtain a more active compound in this system would be derived from Friedlos.

For the above reasons, it is believed that the bromomesylate compounds of formula IIIb are neither disclosed nor suggested by Friedlos, either alone or view of Patani. There would have been no motivation to modify the compounds 12-16 to make compounds in which X and Y must be different instead of the same. There is certainly no suggestion in Friedlos which would motivate one of ordinary skill to replace a bromine with a mesylate with any expectation that the resulting compound would have viable activity.

The above –discussed deficiencies of Friedlos are not cured by Patani. Patani merely provides a general teaching relating to bioisosterism in drug design.

Patani does nothing to motivate the skilled artisan to move from an active symmetric structure to an asymmetric structure with any expectation of viable activity. In particular, Patani provides no disclosure or suggestion which would have motivated replacing a bromine with a mesylate in compound 13 of Friedlos to yield a bromomesylate compound of formula IIIb to counter the Friedlos teaching away from such a substitution.

For all of the above reasons, it is believed that the invention as now claimed is patentably distinguished over Friedlos and Patani, either taken singly or in combination. Withdrawal of the obviousness rejection is respectfully requested.

II. CLAIM AMENDMENTS

The claim amendments effected herewith are as follows:

Claims 1 and 6: canceled without prejudice.

Claim 3: now directed only to the third compound, namely 2-((2-Bromoethyl)-2-{[(2-hydroxyethyl)amino]carbonyl}-4,6-dinitroanilino)ethyl methanesulfonate.

Claim 4: rewritten in independent form.

Claim 8: rewritten to refer to definitions in rewritten claim 4.

Claims 9 and 10: amended to depend from amended claim 8, not claim 6.

Claim 11: amended to refer to formula IIIb (not formula IIb), and to depend from claim 8, not claim 6.

Claim 16: amended to refer to formula IIIb, not formula IIb (2 instances).

Claim 19: amended to refer to formula IIIb, not formula IIb, and to refer to rewritten claim 4, not claim 1.

DENNY et al
Appl. No. 10/529,772
May 8, 2008

No new matter is entered.

Favorable action is awaited.

Respectfully submitted,

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